production of a procollagen in a whole plant or non-human mammal. The Examiner asserts that the present specification does not provide a nexus between the art recognized limitations of producing a transgenic organism with the desired gene expression and phenotype, and the unpredictability recognized in the art of trangenics. Applicant respectfully submits that this is not the case.

The court in Wands established eight criteria to be used in determining whether undue experimentation would be required to practice a claimed invention. These criteria are referred to below.

The quantity of experimentation necessary

Applicant acknowledges that a certain amount of experimentation would be necessary in order to put the invention into practice to produce transgenic plants or animals. That said, this level of experimentation is, to a great extent, inherent in the production of such plants or animals, and does not indicate any insufficiency in the disclosure of the application.

It is know that a certain degree of failure is to be expected during the production of transgenic animals and plants since the technology involved does not result in incorporation of exogenous material at each attempt. Thus

it is normal, and would be expected by a person skilled in the art, that experiments must be conducted to identify plants or animals in which the required exogenous material has been successfully incorporated. To this end, it is normal to conduct further experiments after introduction of exogenous genetic material to confirm the presence of the chosen material. Such "typing" is a recognized part of the production of transgenic plants and animals, and may be readily undertaken using convention laboratory procedures such as gel electrophoresis, DNA ("Southern") blotting and polymerase chain reaction (PCR) that would be well known to a person of skill in the art.

The Examiner states on page 6 of the Office Action that "[t]he question is, can one skilled in the art envision the distinguishing characteristics of the claimed animals without an actual reduction to practice". He then further suggests that it is important to demonstrate that "one skilled in the art could distinguish the claimed transgenic animal from a normal animal".

In response to these points, Applicant submits that the skilled person would immediately appreciate that the most appropriate way in which a transgenic animal could be identified and distinguished from a normal animal would be by using the techniques described above to investigate the

presence of the introduced exogenous genetic material, and/or the expressed product of such material. Such investigations would reveal the genotype and/or phenotype of the animal, and thereby indicate whether or not the exogenous genetic material had been correctly incorporated in order to produce a transgenic animal according to the invention.

Determining those plants or animals in which exogenous material of interest has been incorporated is a recognized and necessary part of all work designed to produce transgenic organisms, and in no way represents an unnecessary burden of experimentation on one wishing to put the invention into practice.

The amount of direction or guidance provided

The Examiner states that "the specification does not disclose any specific detail of expressing the procollagen chain, the expected effect of introducing the nucleic acid, nor if/what cellular material it expects to modify in a transgenic organism".

Pages 10 and 11 of the specification contain directions to a person wishing to effect the invention by production of a transgenic plant or animal. These pages

indicate types of transgenic animals that can be particularly suited to effecting the invention.

For instance, the paragraph spanning pages 10 and 11 teaches that it is desirable to produce non-human placental mammals expressing the novel procollagens of the invention, and that ungulates in particular can be used as the transgenic animals. The specification also teaches that procollagens of the invention can be expressed in the mammary glands of transgenic mammals in order to facilitate the harvesting of the expressed procollagens from the milk. The specification also discloses that the procollagens can be expressed in other body fluids or body tissues, such as eggs. The paragraph starting at line 6 of page 11 further indicates that transgenic plants or animals according to the invention can preferably co-express prolyl-4-hydroxylase in order to achieve proper post-translational modification of the procollagens produced.

In view of these disclosures, Applicant respectfully submits that the Examiner's contention is incorrect.

When considering the amount of direction or guidance provided by the specification, consideration should be given the knowledge of a person skilled in the art, at the priority date of the application. Such a skilled person would have had access to numerous published documents

describing methods of producing many varieties of transgenic plants and animals, including specific examples of expression and secretion of exogenous proteins by mammary tissue, as illustrated by the representative selection of prior art documents set out below. The skilled person would be able to consider the teaching of the specification and select the most suitable transgenic plant or animal model for their intended use of the procollagens. Once the skilled person had selected their intended transgenic species, they would be able to refer to published descriptions of transgenic plant and animal production in order to find the most suitable methodology to create the desired transgenic organism.

The presence or absence of working examples

The instant specification does not contain working examples of transgenic plant or animals expressing novel procollagens of the invention. However, it would be well within the capabilities of a person skilled in the art to apply the teachings of the application in order to produce a transgenic organism according to the invention.

By way of example, enclosed is a copy of a paper published by Applicant (after the priority date) on

"Expression of an engineered form of recombinant procollagen in mouse milk".

The nature of the invention

As indicated above, the production of transgenic plants and animals represents a field of art in which a certain degree of experimentation (such as typing by gel electrophoresis, blotting, PCR, etc.) is required in order to confirm incorporation of exogenous genetic material of interest. This requirement should be considered when assessing what constitutes an unnecessary burden of experimentation.

Equally, it is recognized in the field that the use of transgenic plants and animals as bioreactors for the production of suitable molecules has notable advantages over the use of cultured cells. For this reason, those producing such plants or animals are typically prepared to accept the burden of testing required to confirm successful production of the transgenic organism.

The advantages of the use of transgenic plants and animals should be considered in evaluating the burden placed on a skilled person by the experimentation required to produce and identify such plants and animals. The very fact that transgenic animals have become such a frequently

used experimental tool illustrates that any burden that exists is one that is generally outweighed by the advantages to be gained.

The state of the prior art

At the priority date of the instant application a great number of methods for the production of transgenic plants or animals were known, including a variety of methods for the incorporation of exogenous material encoding procollagens. Indeed, the example of Ruggiero et al cited by the Examiner illustrates the fact that the production of transgenic plants expressing procollagen was known at the time.

The selection listed below contains a number of further documents from the prior art (including reviews) describing suitable techniques for the production of transgenic animals. All of these documents were available to the skilled person at the priority date. In addition, there existed a wealth of data regarding tissue-specific expression of transgenes, for example in cells of the mammary gland.

It was, at the priority date, well known to use the mammary gland of transgenic mammals as bioreactors for the expression of exogenous proteins. Examples of references

describing suitable methodologies by which transgenic animals expressing and secreting human proteins from mammary tissue include Carver et al, Prunkard et al and Van-Cott et al (details provided below). These references illustrate that, at the priority date, published documents were available to the skilled person describing protocols by which relatively high levels of secreted human proteins could be produced in the milk of diverse species such as sheep, mice and pigs.

Based upon the prior art available at the priority date, a person of normal skill in the art would have had no difficulty in selecting or designing a suitable method for producing a transgenic plant or animal capable of expressing the novel procollagens of the invention.

The relative skill of those in the art

The nature of the invention means that the relevant field of the art is one in which the skilled person is likely to be of at least post-graduate, and more likely post-doctoral, education. Those involved in research likely to involve the production of transgenic plants or animals are familiar with the need to undertake literature searches to identify up to date information regarding the research field in question. As such, it should be expected

that those in this field would have been aware of, and have had ready access to, prior art including, and in excess of, that outlined below at the priority date of the instant application.

The examples of the prior art listed below provide details of a number of methods by which a skilled person could produce a suitable transgenic plant or animal expressing the procollagens of the invention.

The skilled person should therefore be expected to have been capable of identifying and putting into practice suitable strategies for the production of a desired transgenic plant or animal capable of expressing the novel procollagens of the invention.

Having produced such a transgenic organism, the skilled person would then have appreciated that the "distinguishing features of the claimed transgenic animals or plants" would be their incorporation of the exogenous genetic material encoding the procollagens of the invention, and the expression of these proteins.

The predictability or unpredictability of the art

Transgenic organism production is a field in which a degree of unpredictability is accepted as unavoidable. It is accepted by practitioners producing transgenic organisms

that a certain "failure rate" is to be expected, and that experimentation must be conducted to identify organisms in which the exogenous material has been incorporated and is correctly expressed.

Applicant therefore submits that the level of experimentation required to produce and select transgenic organisms successfully expressing the procollagens of the invention does not represent an undue burden on the skilled person.

The breadth of the claims

Given the ease with which one skilled in the art would be able to produce a transgenic plant or animal expressing the novel procollagens of the invention, Applicant submits that the breadth of the claims covering transgenic organisms is justified in this case.

Illustrative examples from the prior art are as follows:

1. Carver et al, "Transgenic livestock as bioreactors: stable expression of human α-1-antitrypsin by a flock of sheep", Bio/Technology 11:1263-1267 (1993).

2. Prunkard et al, "High level expression of recombinant human fibrinogen in the milk of transgenic mice", Nature Biotechnology 14:867-871 (1996).

3. Van-Cott et al, "Affinity purification of biologically active and inactive forms of recombinant human protein C produced in porcine mammary gland", J. Mol.. Recognit. 9:407-414 (1996).

4. Wright et al, "High level expression of active human α-1-antitrypsin in the milk of transgenic sheep", Bio/Technology 9:830-834 (1991).

5. Romagnolo and DiAugustine, "Transgenic approaches for modifying the mammary gland to produce therapeutic proteins", Environ. Health Perspect. 102:846-851 (1994).

6. Echelard, "Recombinant protein production in transgenic animals", Current Opinion in Biotechnology 7:536-540 (1996).

7. Charreau et al, "Transgenesis in rats: technical aspects and models", Transgenic Res. 5:223-234 (1996).

8. Colman, "Production of proteins in the milk of transgenic livestock: problems, solutions, and successes", Am. J. Clin. Nutr. 63:6392-645s (1996).

9. Velander et al, "Transgenic livestock as drug factories", Sci. Am. 276:70-74 (1997).

10. Rosen et al, "The mammary gland as a bioreactor: factors regulating the efficient expression of milk protein-based transgenes",, Am. J. Clin, Nutr. 63:627s-632s (1996).

11. Lee et al, "An efficient expression of human growth hormone (hGH) in the mile of transgenic mice using rate beta-casein/hGH fusion genes", Appl. Biochem. Biotechnol. 56:211-222 (1996).

12. Houdebine, "The production of pharmaceutical proteins from the milk of transgenic animals", Reprod. Nutr. Dev. 35:609-617 (1995).

In view of the above, reconsideration is requested.

Claims 31-50 stand rejected under 35 USC 112, second paragraph. The rejection is traversed.

The Examiner contends that claim 31 and dependent claims, are unclear. The Examiner's contention is based upon the perceived lack of clarity in the phrase "said pro-α chains for assembly into said first procollagen with other pro-α chains having said activity".

Respectfully, no basis for the rejection is seen. Antecedent basis for the phrase "said pro-α chain for assembly into said first procollagen" is found at lines 4 and 5 of claim 31 (see also lines 8 and 9). Activity is referenced in line 10. Accordingly, no revision is believed necessary and reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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